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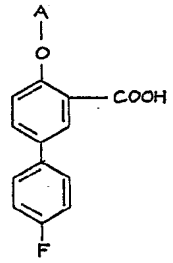
(54) 4-(4-FLUOROPHENYL)PHENYL ACYLATES AND THEIR PRODUCTION AND USE

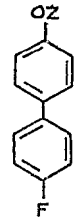
(71) We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a new method of obtaining 5 - (4 - fluorophenyl) - salicylic acid and its - acetyl derivative, which form part of the invention claimed in the specification of our copending application No. 11178/67 (1175212), and which have the formula (I):

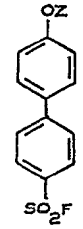


where A is either a hydrogen atom or an acetyl group. This invention is also concerned with novel intermediates produced in the process and methods for obtaining them. 5 - (4 - Fluorophenyl)salicylic acid and its O - acetyl derivative are useful as anti-inflammatory agents, are effective in the prevention and inhibition of oedema and granuloma tissue formation, and have a useful degree of antipyretic and analgesic activity.

The new compounds of the present invention have the general formula:



where Z is an acyl radical, preferably benzoyl. In accordance with the present invention, the new compounds are prepared by treating a compound of general formula:



(which are claimed in and may be prepared by processes described and claimed in the specification of our copending application No. 13256/70 Serial No. 1209539) with a transition metal or a complex thereof as a catalyst. Representative of suitable catalysts are tris - (triphenylphosphine)rhodium fluoride, tris - (triphenylphosphine)rhodium chloride, tetrakis(triphenylphosphine)ruthenium dichloride, bis(triphenylphosphine)ruthenium carbonyl chloride, cobalt carbonyl, platinum and palladium catalysts. Desirable reaction rates are attained at a temperature in the range of from 25°C to 400°C. The reaction product is recovered by crystallization and subsequent fil-

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tration, or by precipitation with a fluid such as petroleum ether, hexane or water, and subsequent filtration.

Also in accordance with the present invention, the novel compounds are subjected to solvolysis to replace the acyloxy group by a hydroxy group and then reacted with carbon dioxide in the presence of a base to introduce a carboxy group ortho to the hydroxy group and produce 5 - (4 - fluorophenyl) - salicylic acid. This compound may be acetylated to give 2 - O - acetyl - 5 - (4 - fluorophenyl)sali - cylic acid. "Solvolysis", in addition to covering various reactions known as "hydrolysis" involving aqueous reaction media, encompasses analogous reactions, such as acidolysis, conducted under substantially anhydrous conditions. Solvolysis can be effected under acidic, neutral or basic conditions. Under neutral conditions, the starting material is mixed with water and a solvent, if desired, and the mixture is allowed to stand until hydrolysis is effected. In most cases, it is desirable to heat the reaction mixture to a temperature in the range of 100°C to 250°C and to conduct the reaction in an autoclave. The rate of reaction is increased when the volume of water is in excess of that of the starting material. When a solvent is used, the preferred ones are those which are water-miscible solvents of the protic type. Among these are the C_{1-6} alkanols, such as methyl and ethyl alcohol, and benzyl alcohol.

The acyl radical Z can also be removed by acid hydrolysis, which is achieved by forming a mixture of the starting material in an aqueous acid. Reaction conditions can vary widely, but it is preferred to use a 10—50% by weight solution of acid and conduct the reaction at a temperature between room temperature and reflux temperature for a period of about 1—24 hours. The reaction mixture may contain, if desired, a solvent that is inert under reaction conditions and such a solvent can be water-miscible or water-immiscible, the former being preferred. Among the preferred water-miscible solvents are protic solvents such as C_{1-6} alkanols, benzyl alcohol, and water-miscible organic acids.

Suitable acids for the purpose of hydrolysis are inorganic or organic acids, preferably strong acids such as hydrochloric, sulfuric and para-toluenesulfonic acids, but the choice of acids is not critical.

Basic hydrolysis can be used in place of acid hydrolysis. It is preferred to use a 10—30% by weight aqueous solution of caustic alkali for basic hydrolysis, with reaction being conducted between room temperature and reflux temperature for a period of from 1 to 4 hours. The reaction mixture can contain either a water-immiscible or water-miscible solvent that is inert under reaction conditions. Among the preferred solvents are C_{1-6} alkanols and benzyl alcohol. Suitable basic compounds are sodium methoxide and potassium butoxide and the strong inorganic bases such as sodium hydroxide, potassium hydroxide and lime, but the choice of the particular basic substance is not critical.

The 4 - (4 - fluorophenyl)phenol thus obtained is converted to 5 - (4 - fluorophenyl) - salicylic acid by reaction with carbon dioxide in the presence of a basic catalyst, e.g. sodium hydroxide, potassium hydroxide, potassium carbonate or sodium carbonate. The desired carboxylation reaction can be carried out at a temperature between the freezing point and the temperature at which undesirable decomposition of either the reactants or the product occurs. The more desirable reaction rates are obtained at a temperature within the range of 100°C to 250°C.

In the final step, 5 - (4 - fluorophenyl) - salicylic acid is reacted with an acetylating agent to produce the desired product. This acetylation step is claimed in the specification of our copending application No. 38482/68 (Serial No. 1204970). Suitable acetylating agents include ketene and compounds represented by the formula:

$$CH_3—CO—X$$

where X is the anion of an acid HX. Representative of the X anion are chloride, bromide, iodide, fluoride, azide, phenoxy, 2,4 - dinitrophenoxy, phenylthio, p - nitrophenylthio, imidazolyl, alkoxy (e.g. methoxy, propoxy or butoxy), hydroxyl, carbodiimidoxyl, α,β - unsaturated alkenoxy (e.g. vinyloxy, allyloxy or isopropenyloxy), aliphatic acyloxy such as acetoxy or propionoxy, alkoxy carbamoyloxy, organophosphato such as alkyl phosphato or dialkyl phosphato, dialkyl arseno, sulfonoxy ($—OSO_3—$), cyanoalkoxy and quaternary ammonium salts such as pyrrolinium.

It is preferred to use as acetylating agents ketone, acetyl chloride, acetyl bromide, acetic anhydride or isopropenyl acetate. With the preferred acetylating agent, the reaction to produce 5 - (4 - fluorophenyl)acetyl salicylic acid proceeds relatively quickly. The acetylation reaction can be carried out in the presence of acidic or basic catalysts which promote acetylation or in the absence of a catalyst. Representative catalysts are bases such as triethylamine and pyridine; and acidic substances such as sulfuric acid and phosphoric acid, boron trifluoride, boron trifluoride - mercuric oxide, p - toluenesulfonic acid, trifluoroacetic acid, sodium acetate, sodium formate and ion-exchange resins. Preferred catalysts are pyridine, sulfuric acid and boron trifluoride.

The reaction is preferably carried out in the presence of a solvent that is not rapidly acetylated. Examples of these solvents are pyridine, benzene, toluene, dimethylformamide, acetone, carbon tetrachloride, chloroform,

methylene chloride, acetic anhydride and acetic acid.

The reaction is carried out at temperature between the freezing point and the point at which undesirable decomposition of the starting material or reaction product occurs. It is preferred to operate at a temperature in the range of from about 0°C. to about 80° C.

Proportions of acetylating agent are not critical since product will be obtained with either reactant present in excess. When excess of acetylation agent is used, the anhydride of the compound of Formula II and acetic acid, may be formed. If it is desired to avoid formation of anhydride, care must be taken not to have present during reaction excessive amounts of the acetylating reactant. However, if some anhydride is formed, it can be subsequently hydrolysed, for example with aqueous acid, to form 5(4-fluorophenyl)acetyl salicylic acid. Preferably, the reaction is carried out with the acetylating reactant being present in amounts ranging from about 10 to about 10,000 percent, preferably from about 100 percent to about 500 percent in excess of the stoichiometric amount.

The reaction product is isolated, recovered and purified by conventional techniques such as by filtration, washing, evaporation, drying and recrystallization.

The following Examples are illustrative of the process of the present invention. Example 1 includes the preparation of the starting material by the process described and claimed in the specification of our copending application No. 13256/70 (Serial No. 1209539); Example 2, step C, shows an acetylation by the process described and claimed in the specification of our copending application No. 38482/68, (Serial No. 1204970).

EXAMPLE 1

Step A

4 - Benzoyloxy - 4′ - fluorosulfonylbiphenyl

One mole (274.3 g.) of 4 - benzoyloxybiphenyl is added over two hours to three moles (300.2 g.) of fluorosulfonic acid at 70°C. When addition is complete, heating at 70°C is continued for 3 hours. The reaction is cooled and poured into ice water. The quenched mixture is extracted with three 1-liter portions of methylene chloride. The extract is washed with water and dried over sodium sulfate. Slow dilution with three liters of petroleum ether precipitates 4 - benzoyloxy - 4 - fluorosulfonylbiphenyl.

Similarly, other 4 - acyloxy compounds can be obtained by using different biphenyl starting materials in the above procedure.

Step B

4 - Benzoyloxy - 4 - fluorobiphenyl

One mole (324.3 g.) of 4 - benzoyloxy - 4′ - fluorosulfonylbiphenyl is heated at 230°C with 3 g. (0.00326 mole) of tris(triphenylphosphine)rhodium fluoride until evolution of sulfur dioxide ceases. The residue is recrystallized from ethanol to give 4 - benzoyloxy - 4 - fluorobiphenyl, m.p. 159—163°C.

Using other 4 - acyloxy starting materials in the foregoing procedure leads to the corresponding 4 - acyloxy - 4′ - fluorobiphenyl products.

EXAMPLE 2

Step A

4 - (4 - Fluorophenyl)phenol

6 g (0.0206 mole) of crude 4 - benzoyloxy - 4′ - fluorobiphenyl is slurried in 100 ml. of 50% aqueous ethanol. 4 g (0.10 mole) of sodium hydroxide is added and the mixture heated to reflux for 5 minutes. The hot solution is cooled and filtered. The filtrate is acidified to pH 2.0 with hydrochloric acid. The precipitated crude 4 - (4 - fluorophenyl) - phenol is filtered, washed with water and dried. Yield, 3.7 g., melting range 145—155°C. The crude phenol is purified by chromatography over silica gel.

Other 4 - acyloxy starting materials can be used in Example 3 to give the same final product.

Step B

5 - (4 - Fluorophenyl)salicylic Acid

100 g of 4 - (4 - fluorophenyl)phenol was finely ground with 300 g. of anhydrous potassium carbonate. The mixture was placed in an autoclave under 700—800 p.s.i.g. of dry carbon dioxide and heated at 235—245°C. for 6 hours. The mixture was cooled and slurried in 1.5 liters of water. The crude potassium 5 - (4 - fluorophenyl)salicylate was filtered. The wet cake was reslurried in 5 liters of water. This mixture was filtered and the filtrate acidified with concentrated hydrochloric acid to precipitate 5 - (4 - fluoro - phenyl)salicylic acid. Yield, 92 g. M.P. 202—204°C.

Step C

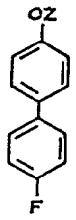
O - Acetyl 5 - (4 - fluorophenyl)salicylic Acid

To one gram (4.3 millimoles) of 5 - (4 - fluorophenyl)salicylic acid and 2 grams (21.2 millimoles) of acetic anhydride was added 40 microliters of concentrated sulfuric acid with agitation at 25°C. The temperature was allowed to rise to 32°C. and was held at 32° C. for 5 minutes. 20 microliters of water was slowly added to the reaction mixture with the temperature being allowed to rise to 40° C. The resultant mixture was stirred for 5 minutes at 40°C. The product, O - acetyl 5 - (4 - fluorophenyl)salicylic acid was crystallized and filtered from the reaction mixture. The filtered product was washed with 10 ml. of water and dried at 60°C. to constant weight. The yield was 1.16 grams of product, m.p. 130—145°C.

One gram of O - acetyl 5 - (4 - fluoro - phenyl)salicylic acid thus produced was dissolved in 70 ml. of hot carbon tetrachloride and cooled to 70°C. 50 mg. of decolorizing charcoal was added to the product which was subsequently refluxed for 15 minutes with agitation. The carbon was collected by filtering the hot solution and the filter cake was washed with 2 ml. of hot carbon tetra - chloride. The combined filtrates and wash were concentrated to 50 ml. in vacuo. The resulting slurry was heated to reflux and cooled at 20°C. per hour to 25°C. After two hours at 25°C., the O - acetyl 5 - (4 - fluoro - phenyl)salicylic acid was filtered, the cake recoveretd and washed with 2 ml. of carbon tetrachloride, and then 5 ml. of hexane and finally dried in vacuo at 60°C. to constant weight. The amount of product recovered was 0.75 gram.

WHAT WE CLAIM IS:—

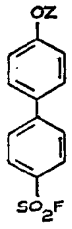
1. A compound of the formula:



in which Z is an acyl radical.

2. The compound claimed in claim 1 in which Z represents a benzoyl radical.

3. The process that comprises reacting a compound of general formula:



in which Z is as defined in claim 1 or 2 with a transition metal or complex thereof to produce a compound as claimed in claim 1 or 2.

4. A process as claimed in claim 3 substantially as described in Example 1 Step B.

5. A process as claimed in claim 3 or 4, including the step of preparing the starting material by a process claimed in the specification of our copending application No. 13256/70 (Serial No. 1209539).

6. The process that comprises subjecting a compound as claimed in claim 1 or 2 to solvolysis to produce 4 - (4 - fluorophenyl) - phenol.

7. A process as claimed in claim 6, in which the solvolysis is effected at 100—250° C in an autoclave.

8. A process as claimed in claim 6, in which the solvolysis is effected with aqueous acid or aqueous caustic alkali.

9. A process as claimed in any one of claims 6—8, including the step of preparing the starting material by a process as claimed in any one of claims 3—5.

10. A process as claimed in claim 6, substantially as hereinbefore described in Example 2 Step A.

11. A process as claimed in any one of claims 6—10, including the further step of reacting the 4 - (4 - fluorophenyl)phenol with carbon dioxide in the presence of a basic catalyst to produce 5 - (4 - fluorophenyl) - salicylic acid and optionally O - acetylating the latter.

12. A process as claimed in claim 11, substantially as hereinbefore described in Example 2.

13. A compound as claimed in claim 1, when prepared by a process as claimed in claim 3, 4 or 5 or an obvious chemical equivalent of such a process.

14. 4 - (4 - fluorophenyl)phenol, when prepared by a process as claimed in any one of claims 6—10 or an obvious chemical equivalent of such a process.

15. 5 - (4 - fluorophenyl)salicylic acid and its 2 - O - acetyl derivative when prepared by a process as claimed in claim 11 or 12 or an obvious chemical equivalent of such a process.

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